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(54) Title: METHOD OF OBTAINING GALLIUN-68 AND USE THEREOF AND DEVICE FOR CARRYING OUT SAIF METHOD

(57) Abstract: The present invention relates to a method of obtaining from a $^{68}Ge/^{68}Ga$ generator and a method of producing ^{68}Ga-radiolabelled complexes using the obtained ^{68}Ga. The invention further relates to a kit, which could be used to obtain ^{68}Ga and a kit, which could be used for the production of ^{68}Ga-radiolabelled complexes.

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METHOD OF OBTAINING GALLIUM-68 AND USE THEREOF AND DEVICE FOR CARRYING OUT SAID METHOD

The present invention relates to a method of obtaining ^{68}Ga from a $^{68}Ge/^{68}Ga$ generator and a method of producing ^{68}Ga-radiolabelled complexes using the obtained ^{68}Ga. The invention further relates to a kit, which could be used to obtain ^{68}Ga and a kit, which could be used for the production of ^{68}Ga-radiolabelled complexes.

PET imaging is a tomographic nuclear imaging technique that uses radioactive tracer molecules that emit positrons. When a positron meets an electron, the both are annihilated and the result is a release of energy in form of gamma rays, which are detected by the PET scanner. By employing natural substances that are used by the body as tracer molecules, PET does not only provide information about structures in the body but also information about the physiological function of the body or certain areas therein. A common tracer molecule is for instance 2-fluoro-2-deoxy-D-glucose (FDG), which is similar to naturally occurring glucose, with the addition of a ^{18}F-atom. Gamma radiation produced from said positron-emitting fluorine is detected by the PET scanner and shows the metabolism of FDG in certain areas or tissues of the body, e.g. in the brain or the heart. The choice of tracer molecule depends on what is being scanned. Generally, a tracer is chosen that will accumulate in the area of interest, or be selectively taken up by a certain type of tissue, e.g. cancer cells. Scanning consists of either a dynamic series or a static image obtained after an interval during which the radioactive tracer molecule enters the biochemical process of interest. The scanner detects the spatial and temporal distribution of the tracer molecule. PET also is a quantitative imaging method allowing the measurement of regional concentrations of the radioactive tracer molecule.

Commonly used radionuclides in PET tracers are ^{11}C, ^{18}F, ^{15}O ^{13}N or ^{76}Br. Recently, new PET tracers were produced that are based on radiolabelled metal complexes comprising a bifunctional chelating agent and a radiometal. Bifunctional chelating agents are chelating agents that coordinate to a metal ion and are linked to a targeting vector that will bind to a target site in the patient's body. Such a targeting vector may be a peptide that binds to a certain receptor, probably associated with a certain area in the body or with a certain disease. A targeting vector may also be oligonucleotide

specific for e.g. an activated oncogene and thus aimed for tumour localisation. The advantage of such complexes is that the bifunctional chelating agents may be labelled with a variety of radiometals like, for instance, ^{68}Ga, ^{213}Bi or ^{86}Y. In this way, radiolabelled complexes with special properties may be "tailored" for certain applications.

^{68}Ga is of special interest for the production of Ga-radiolabelled metal complexes used as tracer molecules in PET imaging. ^{68}Ga is obtained from a $^{68}Ge/^{68}Ga$ generator, which means that no cyclotron is required. ^{68}Ga decays to 89% by positron emission of 2.92 MeV and its 68 min half life is sufficient to follow many biochemical processes *in vivo* without unnecessary radiation. With its oxidation state of +III, ^{68}Ga forms stable complexes with various types of chelating agents and ^{68}Ga tracers have been used for brain, renal, bone, blood pool, lung and tumour imaging.

However, the use of ^{68}Ga obtained from a $^{68}Ge/^{68}Ga$ generator for the production of ^{68}Ga-radiolabelled metal complexes used as PET tracer molecules may cause problems. ^{68}Ga eluate from a $^{68}Ge/^{68}Ga$ generator often contains ^{68}Ge which lead to low radionuclide purity of ^{68}Ga-radiolabelled metal complexes produced from the ^{68}Ga eluate. Furthermore, the eluate also contains so-called pseudo carriers, i.e. other metal cations like Fe^{3+}, Al^{3+}, Cu^{2+}, Zn^{2+} and In^{3+}, which compete with $^{68}Ga^{3+}$ in the subsequent complex formation reaction and eventually decrease the specific activity. A further disadvantage is, that ^{68}Ga eluate from a $^{68}Ge/^{68}Ga$ generator has a low ^{68}Ga concentration, i.e. in the picomolar to nanomolar range. As a consequence, the amount of chelating agent in a subsequent ^{68}Ga-radiolabelling reaction has to be high for the reaction to take place, which in turn leads to low specific activity. A high amount of chelating agent is especially problematic when ^{68}Ga-radiolabelled PET tracers that comprise a bifunctional chelating agent, i.e. a chelating agent linked to a targeting vector are produced as the patient will receive an unfavourable high amount of these tracers.

J. Schuhmacher et al. Int. J. appl. Radiat. Isotopes 32, 1981, 31-36 describe the use of a Bio-Rad AG 1 x 8 anion exchanger for treating the 4.5 N HCl ^{68}Ga eluate obtained from a $^{68}Ge/^{68}Ga$ generator in order to decrease the amount of ^{68}Ge present in the eluate. 4 mL water was used to eluate the anion exchanger. A disadvantage of

this method is the high volume of water, which is necessary to eluate the ^{68}Ga from the anion exchanger. In order to use this eluate for the production of ^{68}Ga-radiolabelled PET tracers that comprise a bifunctional chelating agent, the eluate needs to be further concentrated, e.g. by evaporation which in turn leads to a decrease of ^{68}Ga activity due to the short half-life of this radionuclide.

There is a need for a method of obtaining ^{68}Ga from a $^{68}Ge/^{68}Ga$ generator in such a way, that ^{68}Ga may be used for the production of ^{68}Ga-radiolabelled metal complexes, especially for the production of ^{68}Ga-radiolabelled PET tracers that comprise a bifunctional chelating agent with a high specific radioactivity.

It has now been found that the use of anion exchangers comprising HCO_3^- as counterions is particularly suitable for the purification and concentration of ^{68}Ga from a $^{68}Ge/^{68}Ga$ generator. Not only the amount of ^{68}Ge present in the eluate could be reduced but also the amount of pseudo carriers. Furthermore, the concentration of $^{68}Ga^{3+}$ could be increased up to a nanomolar to micromolar level. Hence, it was possible to reduce the amount of chelating agent in a subsequent complex formation reaction, which considerably increased the specific radioactivity. This result is important for the production of ^{68}Ga-radiolabelled PET tracers that comprise a bifunctional chelating agent; i.e. a chelating agent linked to a targeting vector, as the increase in specific radioactivity enables the reduction in amount of such tracers when used in a patient.

The invention thus provides a method of obtaining ^{68}Ga by contacting the eluate from a $^{68}Ge/^{68}Ga$ generator with an anion exchanger comprising HCO_3^- as counterions, and eluting ^{68}Ga from said anion exchanger.

$^{68}Ge/^{68}Ga$ generators are known in the art, see for instance C. Loc'h et al, J. Nucl. Med. 21, 1980, 171-173 or J. Schuhmacher et al. Int. J. appl. Radiat. Isotopes 32, 1981, 31-36. ^{68}Ge may be obtained by cyclotron production by irradiation of, for instance $Ga_2(SO_4)_3$ with 20 MeV protons. It is also commercially available, e.g. as ^{68}Ge in 0.5 M HCl. Generally, ^{68}Ge is loaded onto a column consisting of organic resin or an inorganic metal oxide like tin dioxide, aluminium dioxide or titanium dioxide. ^{68}Ga is eluted from the column with aqueous HCl yielding $^{68}GaCl_3$. Thus,

^{68}Ga is in the form of $^{68}Ga^{3+}$, which could be used in the synthesis of ^{68}Ga-radiolabelled complexes, e.g. for the production of ^{68}Ga-radiolabelled PET tracers.

Suitable columns for $^{68}Ge/^{68}Ga$ generators consist of inorganic oxides like aluminium dioxide, titanium dioxide or tin dioxide or organic resins like resins comprising phenolic hydroxyl groups (US-A-4264468) or pyrogallol (J. Schuhmacher et al., Int. J. appl. Radiat. Isotopes 32, 1981, 31-36). In a preferred embodiment, a $^{68}Ge/^{68}Ga$ generator comprising a column comprising titanium dioxide is used in the method according to the invention.

The concentration of the aqueous HCl used to elute ^{68}Ga from the $^{68}Ge/^{68}Ga$ generator column depends on the column material. Suitably 0.05 to 5 M HCl is used for the elution of ^{68}Ga. In a preferred embodiment, the eluate is obtained from a $^{68}Ge/^{68}Ga$ generator comprising a column comprising titanium dioxide and ^{68}Ga is eluted using 0.05 to 0.1 M HCl, preferably about 0.1 M HCl.

In a preferred embodiment of the method according to the invention, a strong anion exchanger comprising HCO_3^- as counterions, preferably a strong anion exchanger comprising HCO_3^- as counterions, is used. In a further preferred embodiment, this anion exchanger comprises quaternary amine functional groups. In another further preferred embodiment, this anion exchanger is a strong anion exchange resin based on polystyrene-divinylbenzene. In a particularly preferred embodiment, the anion exchanger used in the method according to the invention is a strong anion exchange resin comprising HCO_3^- as counterions, quaternary amine functional groups and the resin is based on polystyrene-divinylbenzene.

Suitably, water is used to elute the ^{68}Ga from the anion exchanger in the method according to the invention.

The ^{68}Ga obtained according to the method of the invention is preferably used for the production of ^{68}Ga-radiolabelled complexes, preferably for the production of ^{68}Ga-radiolabelled PET tracers that comprise a bifunctional chelating agent, i.e. a chelating agent linked to a targeting vector.

Thus, another aspect of the invention is a method for producing a ^{68}Ga-radiolabelled complex by

a) obtaining ^{68}Ga by contacting the eluate from a $^{68}Ge/^{68}Ga$ generator with an anion exchanger comprising HCO_3^- as counterions and eluting $^{68}Ga^{3+}$ from said anion exchanger, and

b) reacting the ^{68}Ga with a chelating agent.

Preferred chelating agents for use in the method of the invention are those which present ^{68}Ga in a physiologically tolerable form. Further preferred chelating agents are those that form complexes with ^{68}Ga that are stable for the time needed for diagnostic investigations using the radiolabelled complexes.

Suitable chelating agents are, for instance, polyaminopolyacid chelating agents like DTPA, EDTA, DTPA-BMA, DOA3, DOTA, HP-DOA3, TMT or DPDP. Those chelating agents are well known for radiopharmaceuticals and radiodiagnosticals. Their use and synthesis are described in, for example, US-A-4647447, US-A-5362 475, US-A-5534241, US-A-5358704, US-A-5198208, US-A-4963344, EP-A-230893, EP-A-130934, EP-A-606683, EP-A-438206, EP-A-434345, WO-A-97/00087, WO-A-96/40274, WO-A-96/30377, WO-A-96/28420, WO-A- 96/16678, WO-A-96/11023, WO-A-95/32741, WO-A-95/27705, WO-A-95/26754, WO-A-95/28967, WO-A-95/28392, WO-A-95/24225, WO-A-95/17920, WO-A-95/15319, WO-A-95/09848, WO-A-94/27644, WO-A-94/22368, WO-A-94/08624, WO-A-93/16375, WO-A-93/06868, WO-A-92/11232, WO-A-92/09884, WO-A-92/08707, WO-A-91/15467, WO-A-91/10669, WO-A-91/10645, WO-A-91/07191, WO-A-91/05762, WO-A-90/12050, WO-A-90/03804, WO-A-89/00052, WO-A-89/00557, WO-A-88/01178, WO-A-86/02841 and WO-A-86/02005.

Suitable chelating agents include macrocyclic chelating agents, e.g. porphyrin-like molecules and pentaaza-macrocycles as described by Zhang et al., Inorg. Chem. 37(5), 1998, 956-963, phthalocyanines, crown ethers, e.g. nitrogen crown ethers such as the sepulchrates, cryptates etc., hemin (protoporphyrin IX chloride), heme and chelating agents having a square-planar symmetry.

Macrocyclic chelating agents are preferably used in the method of the invention. In a preferred embodiment, these macrocyclic chelating agents comprise at least one hard donor atom such as oxygen and/or nitrogen like in polyaza- and polyoxomacrocycles. Preferred examples of polyazamacrocyclic chelating agents include DOTA, TRITA, TETA and HETA with DOTA being particularly preferred.

Particularly preferred macrocyclic chelating agents comprise functional groups such as carboxyl groups or amine groups which are not essential for coordinating to Ga^{3+} and thus may be used to couple other molecules, e.g. targeting vectors, to the chelating agent. Examples of such macrocyclic chelating agents comprising functional groups are DOTA, TRITA or HETA.

In a further preferred embodiment, bifunctional chelating agents are used in the method according to the invention. "Bifunctional chelating agent" in the context of the invention means chelating agents that are linked to a targeting vector. Suitable targeting vectors for bifunctional chelating agents useful in the method according to the invention are chemical or biological moieties, which bind to target sites in a patient's body, when the ^{68}Ga-radiolabelled complexes comprising said targeting vectors have been administered to the patient's body. Suitable targeting vectors for bifunctional chelating agents useful in the method according to the invention are proteins, glycoproteins, lipoproteins, polypeptides like antibodies or antibody fragments, glycopolypeptides, lipopolypeptides, peptides, like RGD binding peptides, glycopeptides, lipopeptides, carbohydrates, nucleic acids, e.g. DNA, RNA, oligonucleotides like antisense oligonucleotides or a part, a fragment, a derivative or a complex of the aforesaid compounds, or any other chemical compound of interest like relatively small organic molecules, particularly small organic molecules of less than 2000 Da.

In a particularly preferred embodiment, macrocyclic bifunctional chelating agents are used in the method according to the invention. Preferred macrocyclic bifunctional chelating agents comprise DOTA, TRITA or HETA linked to a targeting vector, preferably to a targeting vector selected from the group consisting of proteins, glycoproteins, lipoproteins, polypeptides, glycopolypeptides, lipopolypeptides, peptides, glycopeptides, lipopeptides carbohydrates, nucleic acids,

oligonucleotides or a part, a fragment, a derivative or a complex of the aforesaid compounds and small organic molecules; particularly preferably to a targeting vector selected from the group consisting of peptides and oligonucleotides.

The targeting vector can be linked to the chelating agent via a linker group or via a spacer molecule. Examples of linker groups are disulfides, ester or amides, examples of spacer molecules are chain-like molecules, e.g. lysin or hexylamine or short peptide-based spacers. In a preferred embodiment, the linkage between the targeting vector and the chelating agent part of radiolabelled gallium complex is as such that the targeting vector can interact with its target in the body without being blocked or hindered by the presence of the radiolabelled gallium complex.

A preferred aspect of the invention is a method for producing a ^{68}Ga-radiolabelled complex by

c) obtaining ^{68}Ga by contacting the eluate from a ^{68}Ge/^{68}Ga generator with an anion exchanger comprising HCO_3^- as counterions and eluting ^{68}Ga from said anion exchanger, and

d) reacting the ^{68}Ga with a chelating agent, wherein the reaction is carried out using microwave activation.

It has been found that the use of microwave activation substantially improves the efficiency and reproducibility of the ^{68}Ga-chelating agent complex formation. Due to microwave activation, chemical reaction times could be shortened substantially; i.e. the reaction is completed within 2 min and less. This is a clear improvement as a 10 minutes shortage of the reaction time saves about 10% of the ^{68}Ga activity. Furthermore, microwave activation also leads to fewer side reactions and to an increased radiochemical yield, which is due to increased selectivity.

Suitably, a microwave oven, preferably a monomodal microwave oven is used to carry out microwave activation. Suitably microwave activation is carried out at 80 to 120 W, preferably at 90 to 110 W, particularly preferably at about 100 W. Suitable microwave activation times range from 20 s to 2 min, preferably from 30 s to 90 s, particularly preferably from 45 s to 60 s.

A temperature control of the reaction is advisable when temperature sensitive chelating agents, like for instance bifunctional chelating agents comprising peptides or proteins as targeting vectors, are employed in the method according to the invention. Duration of the microwave activation should be adjusted in such a way, that the temperature of the reaction mixture does not lead to the decomposition of the chelating agent and/or the targeting vector. If chelating agents used in the method according to the invention comprise peptides or proteins, higher temperatures applied for a shorter time are generally more favourable than lower temperatures applied for a longer time period.

Microwave activation can be carried out continuously or in several microwave activation cycles during the course of the reaction.

Another aspect of the invention is a kit for obtaining ^{68}Ga from a $^{68}Ge/^{68}Ga$ generator, which comprises a generator column and a second column that comprises an anion exchanger comprising HCO_3^- as counterions.

In a preferred embodiment, the kit further comprises means to couple the columns in series and/or aqueous HCl to elute the ^{68}Ga from the generator column and/or water to elute the ^{68}Ga from the anion exchanger column. The HCl and the water are preferably aseptically and in a hermetically sealed container.

In another preferred embodiment, the kit according to the invention further comprises a chelating agent, preferably a bifunctional chelating agent, i.e. a chelating agent linked to a targeting vector.

Examples

Example 1:

0.1 M HCl (5-6 mL) was used to elute ^{68}Ga from a $^{68}Ge/^{68}Ga$-generator with a titanium dioxide column. The eluate was acidified with HCl and applied to a cartridge containing a strong basic anion exchange resin based on polystyrene-divinylbenzene comprising HCO_3^- as counterions and quaternary amine functional groups (SPE cartridge Chromafix 30-PS-HCO_3, Macharey-Nagel, Germany). Over 99% of the ^{68}Ga activity was retained on the resin and then eluted with 200 μl of H_2O.

Comparative Example 1a

The eluate obtained according to Example 1 was applied to cartridges containing a strong basic anion exchange resin comprising Cl^- as counterions and quaternary amine functional groups (SAX SPEC, 50 mg, 1 mL, Isolute, UK and SAX SPEC, 15 mg, 3 mL, NTK kemi, USA). Both anion exchangers did not show any ^{68}Ga activity retention.

Comparative Example 1b

The Cl^- counterions of the cartridges used in Comparative Example 1a were exchanged with OH^- counterions and the Example was carried out as described in Example 1a. The retention of ^{68}Ga activity was 10 – 20 %.

Example 2:

Comparative study of ^{68}Ga-radiolabelling of DOTA-D-Phe^1-Tyr^3 – Octreotide (DOTA-TOC).

^{68}Ga obtained according to the method of the invention and ^{68}Ga obtained from a $^{68}Ge/^{68}Ga$-generator without further anion exchanger-treatment are used for ^{68}Ga-radiolabelling of DOTA-D-Phe^1-Tyr^3 – Octreotide (DOTA-TOC).

2a) ^{68}Ga – radiolabelling of DOTA-TOC

Sodium acetate was added to the eluate from the ^{68}Ge/^{68}Ga-generator (36 mg to 1 mL) to adjust a pH of approximately 5.5 and the mixture was vortexed well. DOTA-TOC (20 nmol) was added and the mixture was heated at 96 °C for 25 min. The reaction mixture was cooled to room temperature and applied to a C-18 SPE-column (HyperSEP S C18), which was then washed with 2 mL H_2O and the product was eluted with ethanol: water 50:50 (1 mL).

The reaction mixture and the product were analysed by HPLC using Vydac RP and Fast Desalting HR 10/10 FPLC gel filtration columns. Specific radioactivity (the amount of radioactivity per unit mass of the peptide) was 1.5 MBq/nmol. Electrospray ionization mass spectrometry, ESI-MS, was performed on Fisons Platform (Micromass, Manchester, UK), using positive mode scanning and detecting $[M+2H]^{2+}$. DOTATOC was detected at m/z =711.26 and authentic Ga-DOTATOC was detected at m/z = 746.0 (calculated m/z = 746.5).

2b) ^{68}Ga – radiolabelling of DOTA-TOC using ^{68}Ga obtained from Example 1

Sodium acetate was added to the 200 µl of ^{68}Ga obtained from Example 1 to adjust a pH of approximately 5.5. The complex formation reaction was carried out as described in Example 2a) using 10 nmol DOTATOC.

The reaction mixture and the product were analysed by HPLC using Vydac RP and Fast Desalting HR 10/10 FPLC gel filtration columns. Specific radioactivity was 5 MBq/nmol. Electrospray ionization mass spectrometry, ESI-MS, was performed on Fisons Platform (Micromass, Manchester, UK), using positive mode scanning and detecting $[M+2H]^{2+}$. DOTATOC was detected at m/z =711.26 and authentic Ga-DOTATOC was detected at m/z = 746.0 (calculated m/z = 746.5).

2c) Results

In the case of the use of ^{68}Ga obtained by the method of the invention, it was possible to decrease the amount of DOTATOC needed for the synthesis of the radiolabelled complex and thus increase the specific radioactivity more than 3 times.

Claims:

1. Method of obtaining ^{68}Ga by contacting the eluate from a $^{68}Ge/^{68}Ga$ generator with an anion exchanger comprising HCO_3^- as counterions and eluting ^{68}Ga from said anion exchanger.

2. Method according to claim 1 wherein the $^{68}Ge/^{68}Ga$ generator comprises a column comprising titanium dioxide.

3. Method according to claim 1 wherein 0.05 to 5 M HCl is used to elute ^{68}Ga from the $^{68}Ge/^{68}Ga$ generator.

4. Method according to claim 2 wherein 0.05 to 0.1 M HCl is used to elute ^{68}Ga from the $^{68}Ge/^{68}Ga$ generator.

5. Method according to claims 1to 4 wherein water is used to elute ^{68}Ga from the anion exchanger.

6. Method according to claims 1 to 5 wherein the anion exchanger is a strong anion exchanger comprising quaternary amine functional groups.

7. Method according to claims 1 to 6 wherein the anion exchanger is a strong anion exchange resin based on polystyrene-divinylbenzene.

8. Method of producing a ^{68}Ga-radiolabelled complex by reacting ^{68}Ga obtained by the method according to claims 1 to 7 with a chelating agent.

9. Method according to claim 8 wherein the chelating agent is a macrocyclic chelating agent.

10. Method according to claims 8 to 9 wherein the chelating agent comprises hard donor atoms, preferably O and N.

11. Method according to claims 8 to 10 wherein the chelating agent is a bifunctional chelating agent

12. Method according to claim 11 wherein the chelating agent is a bifunctional chelating agent comprising a targeting vector selected from the group consisting of proteins, glycoproteins, lipoproteins, polypeptides, glycopolypeptides, lipopolypeptides, peptides, glycopeptides, lipopeptides, carbohydrates, nucleic acids, oligonucleotides or a part, a fragment, a derivative or a complex of the aforesaid compounds and small organic molecules.

13. Method according to claims 8 to 12 wherein the reaction is carried out using microwave activation.

14. Method according to claims 8 to 13 for the production of ^{68}Ga-radiolabelled PET tracers.

15. Kit for the preparation of ^{68}Ga from a ^{68}Ge/^{68}Ga generator, which comprises a generator column and a second column that comprises an anion exchanger comprising HCO_3^- as counterions.

16. Kit according to claim 15 further comprising means to couple the columns in series.

17. Kit according to claims 15 to 16 further comprising aqueous HCl to elute the ^{68}Ga from the generator column and/or water to elute the ^{68}Ga from the anion exchanger column, preferably, the HCl and the water being aseptically and in a hermetically sealed container.

18. Kit according to claims 15 to 17 further comprising a chelating agent, preferably a bifunctional chelating agent.

19. Use of a kit according to claim 18 for the production of ^{68}Ga-radiolabelled PET tracers.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 071 490 A (MCBRIDE WILLIAM J ET AL) 6 June 2000 (2000-06-06)	8
A	column 3, lines 7-40 column 6, lines 15-24	1,15,19
X,P	WO 03/059397 A (MCCALL JOHN DOUGLAS ; IMMUNOMEDICS INC (US)) 24 July 2003 (2003-07-24)	8
	page 10, paragraph 4 - page 11, paragraph 2	
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 September 2004	15/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Polesak, H

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/001548

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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